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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,251	12/07/2004	Phillip Mark Hogarth	5644AL-1	2961

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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,251	HOGARTH ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 7-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, and 7-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 2/22/07 and the supplemental amendment and response received on 3/22/07 have both been entered. Claims 4, 6, and 13-42 are canceled. Claims 1-3, 5, and 7-12 are pending and under examination in the instant application. Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Claim Rejections - 35 USC § 112

The rejection of claims 1-3, 5, and 8-12 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in view of the amendments to the claims which are now limited to transgenic mice and further in view of the evidence provided in the form of prior art references by Wooley et al. and Hom et al. that the basis for CIA resistance versus susceptibility in mice was known at the time of filing, and that several "resistant" mouse strains had been identified.

The rejection of claims 1-3, 5 and 7-12 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is withdrawn over amended claim 7, limited to a C57BL/6 X SJL transgenic mouse, in view of the amendments to claim 1 which limit the autoimmune disease to one caused by aberrant immune complex clearance/formation/ inflammation, and maintained in part over claims 1-3, 5, and 8-12. Applicant's amendments to the claims and arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

It is noted that based on the claim amendments, previously raised issues relating to the genus of rodents, the genus of autoimmune diseases, and the genus of cells derived from the transgenic mouse to be used in the screening methods is withdrawn. However, the rejection of record stands regarding the scope of enablement for making a transgenic mouse as claimed from any CIA resistant mouse strain such that the resulting mouse has a phenotype of aberrant immune complex formation/clearance/inflammation related to autoimmune diseases and in particular SLE, or arthritis, and can be used in the instant methods to screen for compounds capable of suppressing the recited phenotype.

The applicant argues that the one of skill in the art knew at the time of filing which mouse strains would show susceptibility versus resistance to CIA, citing Wooley et al. and Hom et al. While this evidence does demonstrate that the skilled artisan at the time of filing could identify mice based on their MHC loci who would exhibit resistance to CIA, the evidence does not overcome the grounds of rejection based on the lack of predictability in the art for using a CIA resistant mouse strain to make a transgenic mouse comprising and expressing a transgene encoding human FcγRIIA receptor, such that the resulting transgenic mouse would exhibit a phenotype comprising susceptibility to an autoimmune disease caused by aberrant immune complex formation/clearance/inflammation, and in particular SLE, or arthritis, and could be used to screen for a compound able to suppress aberrant immune complex formation/clearance/inflammation.

As noted in the previous office actions, the specification does not provide any specific guidance for mouse strains other than the F1 C57Bl/6 X SJL mouse that becomes susceptible to any autoimmune disease caused by aberrant immune complex activity, including collagen-

induced arthritis, following transgenic expression of human FcγRIIA receptor. The applicant argues that it would be routine to make transgenic mouse using various strains of mice resistant to CIA. The applicant then argues regarding the unpredictability of the resulting phenotype that the claims have been amended to limit the phenotype to autoimmune diseases caused by aberrant immune complex formation/clearance/inflammation and that the specification provides evidence in the working examples that transgenic mice expressing human FcγRIIA receptor show susceptibility to CIA, spontaneous development of arthritis, and symptoms of SLE.

In response, the previous office action provided scientific reasons supported by citations from the prior art to show that the skilled artisan would not have been able to predict the phenotype of a transgenic mammal *a priori*. In particular, the previous office action stated that the manufacture of transgenic animals with a given phenotype are sensitive to factors such as the integration site of the transgene, copy number as well as the genetic background of the animal used. This observation is supported by Houdebine et al., who states that "numerous experiments have shown that the level and specificity of expression of a gene construct used as a transgene cannot be easily predicted" {Houdebine et al. (2000) Transgenic Research 9:305-320; pg. 309, col. 2:The expression of transgenes}. Further, Houdebine et al. states that the potency of any transgene can only be estimated in transgenic animals and the level of expression of transgenes in mice is not predictive of their levels in other animals (pg. 310, col. 1, pgph 2). Finally, Houdebine et al. states that another well known problem with transgenesis is leaky expression of the transgene in various tissues in which the utilized promoter is not expected to work because of ectopic expression due to a position effect (pg. 310, col.1, pgph 3). See also Kolb et al., who states that "the expression of foreign genes in transgenic animals is generally unpredictable as

transgenes integrated at random after pro-nuclear injection into fertilized oocytes" because of inhibition by neighboring chromatin {Kolb et al. (1999) Gene 227:21-31; Abstract}. Sigmund, C., concurs, reporting that variation in the genetic background contributes to the unpredictability of the resulting phenotypes of transgenic or gene-targeted animals {Sigmund, C., (2000) Arterioscler. Thromb. Vasc. Biol., p. 1425-1429}. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (e.g. abstract). Based on this evidence, the specification's disclosure of a single transgenic mouse strain, a transgenic F1 C57Bl/6 X SJL mouse expressing human FcγRIIA receptor with the phenotype of reduced resistance to collagen-induced arthritis, does not provide sufficient enablement or guidance for making other mouse strains with the same phenotype. Further, the evidence cited above makes it clear that the skilled artisan did not consider it "routine" to make a transgenic mammal, or even a mouse, with a particular phenotype.

Regarding the teachings of McKenzie et al., the previous office action noted that the specification in fact only provides guidance for the transgenic mice originally reported by McKenzie et al. These mice are C57BL/6 X SJL mice. McKenzie et al. does not teach or suggest that other strains of CIA resistant mice expressing the same transgene would share the same phenotype. It is also noted that the applicants have stated on page 6 of their response, "[t]he human FcγRIIA receptor transgenic mouse is of a C57/Bl6 X SJL background, which has a MHC subtype of H-$2^{b/s}$ (see, e.g. page 18 lines 10 to 12), **which is, of course, why it was so surprising that the presence of the FcγRIIA transgene rendered the mouse susceptible to**

CIA" (Applicant's response, page 6, lines 4-7, emphasis added). As such, the applicant appears to recognize that the phenotype observed in the C57BL/6 X SJL transgenic mouse would not have been *a priori* based on the resistant nature of to C57/Bl6 X SJL mouse strain. As such, neither applicant's specification nor the prior art, including McKenzie et al., supports applicant's position that it would not have required undue experimentation in view of the unpredictability in the art of making transgenic mice with particular phenotypes.

Thus, applicant's amendments, arguments, and evidence, do not overcome the rejection of record. Based on the specification as filed, the specification in only enabling for the claimed methods wherein the transgenic mouse is derived from an F1 C57Bl/6 X SJL mouse strain.

Claim Rejections - 35 USC § 103

The rejection of claims 1-2, 5, and 7-9 under 35 U.S.C. 103(a) as being unpatentable over McKenzie et al. (1999) J. Immunol. 162: 4311-4318. McKenzie et al. is maintained. Applicant's amendments and arguments have been fully considered by have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant argues that McKenzie et al. does not teach or suggest that transgenic mice expressing human FcγRIIA receptor spontaneously develop a systemic autoimmune disease caused by aberrant immune complex formation/clearance/inflammation, such as rheumatoid arthritis and SLE, and further that the thrombocytopenia observed by McKenzie was observed after administration of exogenous material and thus was not spontaneous. In response, the claims as amended contain no limitation that the transgenic mice *spontaneously* develop an autoimmune

disease caused by aberrant complex formation/clearance/inflammation. The claims recite that the transgenic mice are *susceptible* to an autoimmune disease caused by aberrant complex formation/clearance/inflammation. Thus, the claims read on both spontaneous and exogenously triggered autoimmunity. It is further noted that only claims 10-12 recite any specific autoimmune diseases such as arthritis or SLE and that these claims have not been included in this rejection.

In addition, McKenzie et al. clearly teaches, "[i]mmune clearance initiated by autoantibodies occurs in a wide range of autoimmune disorders. [s]tudies of the immune destruction of blood cells, such as platelets in immune thrombocytopenia, have served as a model for exploring the pathophysiology of these disorders.... [t]he development of immune thrombocytopenia requires two pathologic steps: 1) formation and sustained production of Ab to a self or neo-Ag and 2) triggering of Ab effector mechanisms that lead to accelerated platelet clearance and/or platelet activation" (McKenzie et al., page 4311, paragraph 1). Thus, McKenzie et al. clearly teaches that immune thrombocytopenia is an autoimmune disorder associated with aberrant immune complex formation and clearance. Further, as noted above, the transgenic mice exemplified in the instant specification and the mice taught by McKenzie et al. are one and the same, a human FcγRIIA receptor transgenic non-human mouse on a C7BL/6 X SJL background (McKenzie et al., abstract; pg. 4312, Materials and Methods, and the instant specification, pg. 12, lines 30-32; pg. 18, lines 15-20). The previous office action also cited McKenzie et al. for teaching that these mice can be used as a model of autoimmune thrombocytopenia, wherein thrombocytopenia is assessed in terms of platelet counts, and provides specific motivation to use the FcγRIIA receptor transgenic mouse to screen therapeutic modalities (pg. 4313, co. 2; pg.

4316, col. 1, Figures 5 and 6, and pg. 4317, col. 2). In particular, McKenzie et al. provides motivation to test therapies that diminish Ab effector mechanisms in human immune thrombocytopenia directed at the expression or function of the FcγRIIA receptor (pg. 4317, col. 1). McKenzie et al. also teaches several compounds with the ability to suppress aberrant immune complex formation, clearance, and inflammation, including glucocorticoids and anti-D Ig (pg. 4311, col. 2) . Thus, in view of the motivation to test therapeutic modalities in the FcγRIIA receptor transgenic mouse provided by McKenzie et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to test compounds such as glucocorticoids and anti-IgD for their ability to suppress aberrant immune complex formation and clearance associated with immune thrombocytopenia by administering them to the FcγRIIA receptor transgenic mouse and to assess the mouse for reduced aberrant immune activity with a reasonable expectation of success.

No Claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER